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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	39

DATE MAILED: 04/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/338,248	LEE, STEPHEN C.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a response filed 1/21/03 as Paper No. 18. In Paper No. 18 claims 6 & 7 were amended and a new claim, claim 9, was added. Claims 5-9 are pending in the instant application.

Receipt is also acknowledged of a second declaration under 35 U.S.C. 1.132 by Dr. Vincent Tropope, along with a color copy of the figure originally presented in the first declaration submitted by Dr. Tropope on 4/22/02 (Paper No. 13). Both declarations and the response filed in Paper No. 18 have been considered in full and found nonpersuasive concerning rejection of the pending claims under 35 U.S.C. 112 1st paragraph for lack of enablement. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is extended to newly added claim 9. This rejection is maintained for reasons of record (Paper No. 8, mailed 4/11/01; in Paper No. 5, mailed 7/17/00; Paper No. 15, mailed 7/16/02) and which are repeated below.**

The instant claims are drawn to methods of treating individuals (humans) with a degenerative disease, disorder or abnormal state of the retina or eye (various examples are

recited in claim 4) comprising implanting retinal stem cells or retinal cells differentiated from retinal stem cells. The following factors have been considered in the rejection.

The nature of the invention. The nature of the invention is *in vivo* treatment of individuals, especially humans with a wide spectrum of degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited to indicate the state of the prior art and the unpredictable nature of the invention. The art at the time of the invention did not recognize retinal stem cells or their use in treatment of degenerative disease, disorder or abnormal physical states of the eye/retina via *in vivo* transplantation. The art does, however, recognize the ability to transplant retinal epithelial cells (RPE cells) (either as a tissue-layer or as individual cells) into the eye of various different animal models, including mammals. RPE cells are one type of cell expected to differentiate from retinal stem cells.

Grisanti et al. (U) teach the transplantation of RPE cells. They teach that normal RPE cells transplanted into the subretinal space of mutant RCS rats survive and rescue photoreceptor cells otherwise destined to undergo degeneration. However, they state that the while these findings are encouraging, the ultimate goal of achieving long-term survival of RPE allografts remains elusive (page 1619). Grisanti et al. also teach that the eye has the rare characteristic of being an immunologically privileged site, but they also caution that the ocular immune privilege is not absolute and that immunologic recognition of allogenic or xenogenic tissues/cells result in the rejection of histo-incompatible grafts. At page 1625, they teach that even autologous tissue/cells may be rejected if the immune system is not suppressed. They teach that RPE cells produce specific auto-antigens that act as strong immunogens that trigger immune reactions that result in rejection of the RPE cells (see page 1624). They teach that ACAID may have a role as

a possible fail-safe mechanism to limit the destructive autoimmune reactions in the privileged sites, but also teach that prolonged ACAID may be accompanied by other detrimental side effects such as fibrosis.

Enzmann et al. (V) teach that while transplantation of RPE cells from embryonic and non-embryonic origins in the subretinal space of different animal models, including the RCS rat has resulted in maintenance of retinal function for long periods of time, such transplantations in humans have yet to be shown to be effective. One reason for this is an immune response to the transplanted cells at the transplantation site. One can detect rejection, indicating that the eye is not absolutely an immunologically privileged site (see for example the abstract). These teachings corroborate those of Grisanti et al. discussed immediately above. At page 182, Enzmann et al. teach that while the immune reaction may be controlled with extensive therapies, transplantation in the subretinal space is performed to improve the quality of life, not to save life. The extensive immunosuppression required may however, endanger the survival of the patient because of its serious side effects. They conclude that many immunological questions must be answered (it is noted that this reference was published two years after Applicant's effective filing date) before extensive efforts in patients are possible and before rejection is no longer a major barrier to success.

Crafoord et al. (W) and Valtink et al. (X), both of which were published in 1999, three years after Applicant's effective filing date, fully corroborate the findings discussed above. They both teach mammalian systems in which strong immunological reactions develop over time that result in the rejection of the transplanted cells. They both teach that this is a significant hurdle that must be overcome before progress can be made in treating patients with disorders of the retina/eye.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. The specification is completely silent with respect to

transplantation of retinal stem cells (isolated from the RPE) or cells that have differentiated from the RPE. The specification fails to teach *in vivo* transplantation of any of the above cell types. Because there are no teachings as to how one may achieve transplantation and the fate of the cells after transplantation; the specification also does not teach the treatment or amelioration of even a single degenerative disease, disorder or abnormal physical states of the eye/retina, such as those enumerated in claim 4. There are no teachings as to how the skilled artisan would overcome any of the obstacles recognized in the art (summarized above) to reliably and predictably treat any disorder of the eye/retina--especially those as widely varied as blindness (which may a result of optic nerve damage, as opposed to a damaged retina) and cancers of the retina. There is not even a suggestion in either the art or the instant specification as to how retinal stem cells (isolated from the RPE) or cells that have differentiated from the RPE may treat disorders with a wide variety of etiologies (nerve damage, viral infection, neoplasia, etc.) The teachings of the specification may be characterized as speculative or prophetic at best with regard to treatment of any condition of the eye/retina.

The breadth of the claims. As mentioned above, the claims are drawn to the treatment of any condition of the eye or retina via transplantation of retinal stem cells or cells that have differentiated from said cells.

The quantity of experimentation. The art recognizes several hurdles to successful transplantation of RPE cells to treat degenerative disorders of the retina, including the problems of immunological reactions that result in the rejection of cells that are transplanted into the eye/retina. The prior art is silent with respect to the transplantation of retinal stem cells, ostensibly because prior to Applicant's disclosure, mammalian retinal stem cells were unknown. Therefore, there is a high degree of unpredictability in the treatment of degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual. This is especially true for

transplantation of retinal stem cells since the art did not recognize this at the time of the invention.

As discussed above, the specification does not provide teachings with regard to the *in vivo* transplantation of retinal stem cells or cells differentiated from retinal stem cells and their fate after transplantation. The specification also fails to teach the treatment or amelioration of even a single degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual.

In order to practice the invention, the skilled artisan would turn to the prior art and teachings of the specification. However, as summarized in the previous two paragraphs, neither the prior art nor the specification provide teachings which enable the skilled artisan to treat degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual. Given the highly unpredictable nature of the invention, the skilled artisan would need to engage in empirical or trial and error experimentation to practice the claimed invention. First the skilled artisan would have to overcome the immune response problem that is well documented in the art, then the artisan would need to establish appropriate transplantation sites, appropriate cell numbers to for each condition found recited in the claims. In addition, the skilled artisan would need to develop appropriate assays to determine which protocols were efficacious (these assays would certainly vary with the condition to be treated). This level of experimentation would clearly be undue on the part of the skilled artisan and as such, the specification is not found to be enabling for the claimed invention.

Response to Arguments

Applicant's arguments filed in Paper No. 18 have been fully considered but they are not persuasive. The response relies in large part on evidentiary declarations provided by one of the inventors, Dr. Vincent Tropepe, for its arguments (Papers No. 13 and 18). The response essentially argues: 1) the examiner has stated in an interview that the claimed methods are not enabled because there is no teaching available at the time of the invention for overcoming the immune response and no proof that the animal model system used by the inventors is art recognized as predictive of success in treating a human animal for any disease, disorder or abnormal state of the retina of the eye, 2) the claims have been amended to explicitly link the disease or disorder to be treated to the retina of the eye, 3) transplantation methods were art-recognized prior to applicants' filing date (i.e. transplantation of cells into the retina of an individual via subretinal or intravitreal injection was art known and does not represent the inventive contribution of the present invention), 4) the mouse model of retinal stem cell transplantation is predictive of success in humans (e.g. the experimental results and opinion supplied by Dr. Tropope in his declarations), 5) four weeks is sufficient time for evaluating the presence or absence of an immune response (e.g. several of the cited references report similar lengths of time in reporting their observations and because the retina is an immune-privileged site), 6) immunosuppressants may be used to alleviate whatever immune response may arise upon transplantation (e.g. immunosuppression is common is all forms of transplantation), and 7) a skilled artisan would recognize that the present invention is useful for the treatment of retinal cell-associated diseases or disorders.

The examiner would like to note that the enablement rejection made herein has never been presented as simply a matter of there being no teaching available at the time of the invention for overcoming the immune response and/or that there is no proof that the animal model system used by applicants is art recognized as predictive of success in humans. These are only factors in a complete Wands analysis that has been made in formulating the instant rejection of the pending claims for lack of enablement, but not the sole basis for making the rejection. It is the combination of factors discussed above in making the rejection that make it clear that it would take undue, unpredictable experimentation of an inventive nature in order to practice the claimed invention in its intended purpose (i.e. treatment of human disease or disorders of the retina). The examiner would also like to note that although claims 5, 8 and 9 do no explicitly state that the method of transplantation is practiced to treat an individual, the only disclosed use for the claimed method is in fact the treatment of a human individual suffering from a disease or disorder of the retina.

With regard to the amendment of the pending claims to explicitly link claims 6-7 to treatment of retina-based diseases or disorders, this amendment of the claims is appreciated and does help to avoid any enablement issues concerning the treatment of non-retinal diseases or disorders. This amendment does not, however, obviate the grounds of rejection discussed herein.

With regard to the assertion that transplantation methods were art-recognized prior to applicants' filing date, this statement is accurate as far as it goes. As indicated in making the rejection, the art recognized at the time of filing the ability to physically transplant retinal epithelial cells (RPEs) into the eye of various animal models, including mammals. The degree of efficacy (i.e. actual therapeutic effect that lasts long-term) demonstrated in the prior at the time

of the invention is not clear, however (see below). The references cited in applicants' response teach methods of transplantation into several different kinds of mammals (e.g. rabbits and rats). It is noted, however, the references of record do not teach the transplantation of RPEs into the eye of the human so that one of skill in the art desiring to practice the claimed invention on a human subject could do so in a predictable manner. In order to practice the claimed invention in humans, one of skill in the art would have to also determine whether the teachings of the cited references concerning transplantation in test animals can be reliably extrapolated to humans (e.g. number and type of cells to be injected, means of injection, etc.).

The assertion that the mouse model of retinal stem cell transplantation is predictive of success is only minimally supported by the results presented by Dr. Tropope in his declarations. In his declaration Dr. Tropope has given his opinion as an expert in the field that the mouse model is accepted by skilled artisans working in the field of retinal cell transplantation as predictive of transplantation success in humans (Paper No. 18, Declaration, paragraph 6). Of the art of record, only the post-filing Grisanti et al reference actually uses the mouse system. The authors use the mouse system in a general way to examine the immune response in mice to different locations for transplanting RPEs into the eye (e.g. subretinal space, anterior chamber, subconjunctival space). Grisanti et al perform their research in the hopes of understanding the immune response in the eye so that someday in the future RPE transplantation may achieve long-term success. Grisanti et al teach "Yet, despite these encouraging successes [in other animal model systems], the ultimate goal of achieving long-term survival of RPE allografts remains elusive." (page 1619, column 2). The Grisanti et al reference does not address a particular disease or disorder of the retina in the mouse and makes no attempt to demonstrate that a

therapeutic response observed in the mouse will necessarily indicate success in humans. In searching the prior art, the examiner has found no instance where an RPE-transplantation approach shown to be efficacious in mice has been shown to be replicated in humans (i.e. necessarily predictive of success).

The data provided by Dr. Tropope do indicate that transplanted retinal stem cells in the mouse move into several layers of the retina and appear to form at least two differentiated cell types (i.e. Muller glial cells and rod cells) based upon co-localization of the donor GFP marker and markers indicative of the mature cell types, as well as cell morphology (e.g. rod cell morphology). This is an encouraging observation, indicating that the retinal stem cells isolated according to the methods of the instant application retain at least some ability to differentiate into different cell types *in vivo*. However, the results presented by Dr. Tropope do not necessarily indicate that the degree of integration and differentiation would be therapeutic for any particular disease in the mouse, much less the human. For example, while the transplanted retinal stem cells appear to differentiate to some degree, there is no actual data that the cells are functional in a way that would necessarily be efficacious (e.g. compensating for a deficiency present in the mouse) or effective over the long term. Applicants point to the results of three references in support of their assertion that the results presented by Dr. Tropope indicate that successful treatment of an individual with a disease or disorder characterized by loss of retinal function can be achieved by transplanting retinal stem cells into the retina of the individual.

The first reference, by He et al (1993), features the transplantation of cultured human RPEs into the eyes of rabbits. He et al observe that the transplanted cells appear to restore function of the RPE layer as evidenced by "the process of phagosomes and phagocytosed outer

segments in the transplanted cells" (Abstract). He et al do observe, after a period of three months, the appearance of macrophages in the subretina of transplanted eyes (e.g. Abstract). He et al conclude "Our results, in conjunction with those of others suggest that graft rejection may not be an insurmountable problem. The donor RPE cells survived several months, developed phagocytic capacity, and triggered only a mild host immunoreaction. Immunosuppressive therapy with drugs such as cyclosporine might well eliminate the latter deleterious response." (page 741, last paragraph). He et al clearly recognize that the observed response is a deleterious response, presaging possible graft rejection, and that it is one that *may not be an insurmountable problem* because immunosuppressive therapy *might* be able to prevent rejection. One of skill in the art, upon reading the totality of the teachings of He et al would necessarily conclude that, while promising, significant hurdles remain to practicing RPE transplantation in rabbits in a predictable manner (e.g. long-term rejection).

Whitely et al (1996) teach the transplantation of RPEs into a rat animal model system, the Royal College of Surgeons (RCS) rat, that has a genetic predisposition for deterioration of the RPE layer in the retinal (e.g. page 100, first paragraph). The authors indicate that the RCS rat is a good model for retinitis pigmentosis and age-related macular degeneration (ARMD). The authors assayed retention of retinal function through measuring the pupillary light reflex (PLR) that is presumable driven by residual photoreceptor population in the peripheral retina. According to the authors, their results confirm the findings of previous studies concerning the efficacy of RPE cell graft techniques in rescuing photoreceptors as well as also providing evidence that the rescued cells affect a minimal visual function (i.e. the PLR) (e.g. page 101, last paragraph). Whitely et al teach, however, that rescue of the photoreceptor activity was not

permanent and that a gradual deterioration continued to occur. Whitely et al did not observe any indication of graft rejection, but did not rule out the possibility such rejection might account for the loss of photoreceptor activity over time (e.g. page 102, column 1). While promising in that the results shows that transplanted RPE cells in an animal model for specific conditions can rescue a *minimal* photoreceptor function (PLR), the data obtained by Whitely et al were only temporary with no concrete explanation as to lack of long-term success (e.g. graft rejection or some unexplained phenomenon.

Sauve et al (1998) is a post-filing reference cited by applicants as supporting the observations made by the applicants and presented by Dr. Tropope in his declarations. Sauve et al use dystrophic Royal College of Surgeons rats in their RPE transplantation experiments and map single and multiunit receptive fields across the surface of the superior collculus following transplantation. Sauve et al demonstrate that the transplantation of RPE cells into either the subretinal space or the intravitreal space results in RPE cell survival and rescue of photoreceptor function. Sauve et al conclude "The present study assumes further importance as transplantation experiments are *considered* in humans and provides a *potential* source of comparison between animal and human studies, particularly with respect to visual field assessment. Clearly, however, to be able to say whether the rat shows retention of *higher visual function*, it will be necessary to examine cortical function and associated acuity measures, and this can be best achieved in coordination with behavioral studies of visual acuity." (examiner's emphasis added) (page 248, last paragraph). Sauve et al evidently view their results as promising with regard to possible future experiments in humans, but also indicate that the level of functional activity seen in their experiments are not necessarily indicative of restoration of "higher" visual function.

Presumably, an indication that higher-level visual function was restored would be suggestive of actually restoring function to such an extent that RPE-transplantation would be efficacious. Thus, the teachings of this post-filing art do not indicate that practicing RPE transplantation in humans to treat retina-based diseases or disorders in humans would necessarily be successful in restoring function.

Applicants continue to assert that 4 weeks is sufficient time in the mouse animal model to conclude that no significant immune response is likely to occur. In support of their argument, the response cites the times post-transplantation used by several of the references of record to measure immune response in different animal model systems (e.g. rabbits, rats, etc.). It is unclear how one is supposed to accurately correlate the post-translational measurements made in rabbits at 3 months in rabbits (He et al, where macrophage infiltration was observed at three months), for example, with those used by applicants in mice (no detected immune response at 4 weeks). It is further noted that the only one of the references that uses the mouse animal model is the post-filing Grisanti et al reference. Grisanti et al made their measurements at 12 days post-implantation (e.g. the Abstract). Although Grisanti et al did not observe a classical immune response and proposed that the subretinal and anterior chamber of the eye might be relatively privileged, the authors indicate that the privilege might not be long-term and that even autologous tissue might be rejected in the absence of immunosuppression (e.g. page 1625, column 2, second paragraph). As for the other animal systems, the response implies that all of the references state that no immune response by inflammatory cells was observed at the different times (page 8, second paragraph of Paper No. 18). This statement is misleading in that a response was seen in at least some instances (e.g. infiltration by macrophages observed by

Crafoord et al). Applicants appear to be making the argument that whatever immune response is seen in the various animal model systems is not a "classical" immune response and consists primarily of large macrophages. As the examiner has pointed out previously, whatever the immune response may be that has been observed, it still remains a problem that must be resolved in order to practice the claimed invention, whether it is considered a "classical" response or not.

It is noted that in asserting that 4 weeks time is sufficient to establish in the mouse model that significant long-term immune response will not occur, applicants' response further implies that the prior art recognizes the retina as an immune-privileged site (page 8, last line of the first paragraph of applicants' response). The issue of whether the art recognized the retina as an immune-privileged site at the time of applicants' invention is not at all clear. For example, in post-filing art He et al refer to the subretina as "relatively" immuno-privileged and suggest the use of immunosuppressants (e.g. page 740-741). If the immune response were not a problem then why suggest the use of immunosuppressants? The response points to experiments by Grisanti et al that show a difference between immune responses when the transplanted cells are injected into the subretinal space as opposed to the non-privileged subconjunctival space. The examiner concedes that Grisanti et al demonstrate that the subretinal space is privileged *relative* to the subconjunctival space. Grisanti et al also teach "It remains to be seen whether RPE-specific ACAID is permanent or can be overcome by long-standing exposure to immunogenic factors. In the last case, even antilogous tissue may be rejected if the immune system is not suppressed. Within the eye, rejection of allografts or immune reactions against autoantigens of local cells may develop in atypical fashion when compared with immune reactions at conventional sites (e.g. Scon)." (page 1625, second paragraph). Thus, the post-filing Grisanti et

al reference makes clear that it was unknown at the time of filing whether any difference in immune response (i.e. ACAID) would be maintained over time in the absence of immunosuppression, making it unpredictable as to whether transplanted RPEs would survive long-term in the absence of immunosuppression.

Applicants' assertion that both short-term and long-term immunosuppression is a common intervention for all forms of transplantation is accurate as far as it goes. It is noted that the cited forms of transplantation (e.g. lung, liver, kidney) all appear to involve transplantation of whole organs when the subject's life is in danger. The retina-based diseases and disorders encompassed by the rejected claims are not life threatening. Enzmann et al teach that in intraocular transplantation a systemic immunosuppression is possible, but the major problem is the possible side effects of the drugs used (e.g. nephrotoxicity, hypertension and hepatotoxicity). The authors teach the problem with the systemic approach for immunosuppression is that while intraocular transplantation is not necessary for the survival of the patient, immunosuppression therapies can endanger the survival of the patient because of the serious side effects. This post-filing reference further teaches that, in the future, local immunosuppression with artificial compounds or with recombinant cytokines will receive more and more attention. Enzmann concludes that "Many immunological questions must be answered, however, before extensive efforts in patients are possible and before rejection is no longer a major barrier to successful retinal transplantation." (page 182, last paragraph). Applicants' own specification does not support the assertion that strategies were known at the time of filing for using immunosuppression in conjunction with retinal transplantation without serious side effects. The specification, in making its argument against conventional approaches for the treatment of retinal

disorders, teaches that the use of immunosuppressants is undesirable because of the negative side effects associated with such treatments (e.g. page 10-23; page 4, lines 7-9). No teaching is provided by the instant specification concerning what compounds and methods could be used in transplantation of retinal stem cells for systemic or local immunosuppression without serious side effects. Thus, in the absence of any specific teachings from the instant specification on how to practice retinal stem cell transplantation with immunosuppressants, and the teachings from the contemporary or post-filing art that the effective use of such immunosuppressants for RPE transplantation was not known, it would have required inventive experimentation in order to determine which immunosuppressants could be administered in which manner in order to practice the claimed invention for therapeutic effect without dangerous side-effects in humans.

The assertion that a skilled artisan would recognize that the present invention is useful for the treatment of retinal cell-associated diseases or disorders is an opinion that is not supported by the references of record. To summarize, for those references in which the transplanted RPE cells have been shown to restore or prolong retinal function, the problem of possible graft rejection is recognized (e.g. He et al), the loss of function over time recognized, if not explained (e.g. Whitely et al), and the lack of a showing of restoration of higher visual function admitted (Sauve et al). Applicants' own post-filing data only show an encouraging ability of transplanted retinal stem cells to form different cell types, but do not show any restoration of retinal function. The references of record make clear that long-term survival of RPE cells at the time of filing was still very much an issue, indicating the need to use immunosuppressants to ensure long-term survival of the transplanted cells. The art of record and the instant specification make clear the negative effects associated with such treatments, and contrary to the assertion in the response, make clear

that administration of immunosuppressants in conjunction with RPE transplantation without negative side effects was not practiced in the art at the time of the invention. Taken together, the art of record make clear that the practice of RPE or retinal stem cell transplantation in humans was not enabled at the time of the invention, even in light of the teachings of the instant specification.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
April 9, 2003